Correlation between HbA1c Levels with Carotid Intima Media Thickness in Newly Diagnosed Type 2 Diabetes Mellitus Patients

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is the most common chronic disease in the world. Macrovascular complications such as cardiovascular and cerebrovascular diseases can be detected early, one of them by using an ultrasound examination to assess carotid intima-media thickness (CIMT). HbA1c examination had a strong predictive value for the occurrence of T2DM complications. HbA1c levels are associated with CIMT in the non-DM group. In the T2DM group there was an increase in CIMT compared to the non DM group. HbA1c levels can be used as a predictor of the progression of CIMT improvement in the T2DM group, but there is no study on populations with newly diagnosed T2DM.
Aims: This study was conducted to find out the correlation between HbA1c in newly diagnosed T2DM and CIMT.
Methods: This was a cross-sectional study with correlation analysis carried out on newly diagnosed T2DM in four Primary Health Centers in the city of Bandung who were randomly selected from July to August 2018. HbA1c measurement was carried out at Dr. HasanSadikin hospital. The CIMT examination was done according to the Manheim Consensus by a cardiologist. Pearson correlation analysis was performed to assess the relationship between those two variables.
Results: This study involved 32 subjects with a median age of 52 (40 - 60) years. The mean value of CIMT was 0.77±0.22 mm, while the median value of HbA1c was 6.7 (5.2-12.3). Bivariate analysis showed a moderate positive correlation between HbA1c and CIMT in newly diagnosed patients with T2DM. ($r= 0.567$, $p<0.001$).
Conclusion: There was a significant positive correlation between HbA1c in newly diagnosed T2DM and CIMT.

Keyword: newly diagnosed type 2 diabetes mellitus; HbA1c; carotid intima-media thickness

INTISARI

Latar Belakang: Diabetes Melitus Tipe 2 (DMT2) merupakan penyakit kronis yang paling banyak ditemui di seluruh dunia. Komplikasi makrovaskular DMT2 berupa penyakit kardiovaskular dan serebrovaskular dapat dideteksi dini, salah satunya dengan menggunakan pemeriksaan USG untuk menilai *carotid intima-media thickness* (CIMT). Pemeriksaan HbA1c memiliki *predictive value* yang kuat untuk terjadinya komplikasi DMT2. Kadar HbA1c memiliki hubungan dengan CIMT pada kelompok non-DM. Pada kelompok DMT2 terdapat peningkatan CIMT dibandingkan dengan kelompok non-DM. Kadar HbA1c dapat digunakan sebagai prediktor progresi peningkatan CIMT pada kelompok DMT2, namun masih belum ada penelitian mengenai hal ini yang khusus pada populasi DMT2 yang baru terdiagnosis.
Tujuan: Penelitian ini dilakukan untuk mengetahui hubungan HbA1c pada penyandang DMT2 yang baru terdiagnosis dengan CIMT.
Metode: Penelitian ini merupakan penelitian potong lintang dengan analisis korelasi yang dilakukan pada penyandang DMT2 yang baru terdiagnosis penelitian dilakukan di empat puskesmas di kota Bandung yang terpilih secara acak pada bulan Juli sampai Agustus 2018. Pengukuran kadar HbA1c dilakukan di laboratorium RSUP Dr. Hasan Sadikin. Pemeriksaan CIMT dilakukan menggunakan teknik yang sesuaidengan Konsensus Manheim oleh ahli jantung konsultan vaskular. Analisis korelasi Pearson dilakukan untuk menilai hubungan antara keduanya.
Hasil: Penelitian ini melibatkan 32 subjek dengan median usia 52 (40 – 60) tahun. Nilai rata-rata CIMT sebesar 0.77±0.22 mm, sedangkan nilai median HbA1c adalah 6.7 (5.2–12.3). Analisis bivariat menunjukan korelasi positif sedang antara HbA1c pada penyandang DMT2 yang baru terdiagnosis dengan CIMT ($r=0.567$, $p<0.001$).
Simpulan: Terdapat hubungan antara HbA1c pada penyandang DMT2 yang baru terdiagnosis dengan CIMT.

INTRODUCTION

Type 2 Diabetes Mellitus is the most prevalent non-communicable chronic disease, World Health Organization (WHO) data showed a marked increase of incidence from 108 million to 422 million cases from 1980 to 2014.[1] The same dataset listed Indonesia as the fifth most numerous T2DM case.[2] These numbers inherently showed that DM and its complications remains as the largest mortality contributor worldwide, with cardiovascular disease the most common cause of death in such population, accounting for half or approximately 4 million annual deathsby the year 2017.[2]

Glycated hemoglobin or HbA1c has long been recommended by American Diabetes Association (ADA) as a diagnostic criteria for T2DM and its level determines glycemic control.[3] HbA1c reflects the mean level of blood glucose within the last three months and has been proven to possess a strong predictive value for detecting T2DM complication.[4]

In retrospect, macrovascular complications in T2DM, that is cerebrovascular and cardiovascular diseases, are the main contributor in mortality and prompt the importance of early detection. One of the modalities that has long been proven for early macrovascular complication detection is ultrasonography for examining CIMT.[5,6]

Recent studies have elaborated the association between HbA1c and cardiovascular diseases.[2] The increase in CIMT is a known marker for subclinical atherosclerosis. Conversely, HbA1c has also been discovered as independent predictor for the progression of CIMT increase in patients with longstanding T2DM. There is no data such relationship in newly diagnosed T2DM patients.

METHODS

This is a cross sectional study aiming to analyze correlation on 32 subjects of newly diagnosed T2DM in primary health facility in Bandung. We

conducted a consecutive sampling in July to August 2018 period.

Subjects eligible for enrollment were those who were newly diagnosed T2DM within under three months period, or over 6 months without routine medication in two consecutive months and aged under 60 years. We exclude those with anemia, history of blood transfusion within the last 3 months prior to enrollment, chronic kidney disease with GFR less than 60 mL/min, on medication affecting the measurements of HbA1c such as aspirin, opioid, antiretroviral, dapson, ribavirin, trimetoprim-sulfamethoxazole, and hydroxyurea.

We conducted blood sampling and CIMT measurement to the subjects. Measurement of HbA1c was performed in HasanSadikin General Hospital central laboratory, and the CIMT measurement was taken by a vascular consultant according to Mannheim criteria.

Statistical analysis was performed using SPSS 21.0, (SPSS Inc, Chicago, IL, USA) We conducted Saphiro-Wilk for normality test, and then analyzed the data using Pearson's method to investigate correlation. Baseline characteristics were presented using sum and percentage for categorical variables. Numerical data were presented based on the distribution normality; for normally distributed data, we use mean and standard deviation and for data with non-normal distribution, we present in median and range. A bivariate analysis was then performed to investigate correlation between HbA1c with CIMT using Pearson's test for data with normal distributionor Rank-Spearman test for data with non-normal distribution. A p-value of <0.05 was considered statistically significant. We then further present the correlation coefficient for correlation coefficient (r) as in Table 3.2. and interrelation between HbA1c with CIMT will be presented in determinant coefficient (R^2).

RESULTS

This study enrolled 32 subjects with baseline characteristics included age, gender, anthropometric parameters such as height, weight, body mass index (BMI), history of hypertension and blood pressure.

Normality test shows that some baseline characteristics i.e. weight, BMI, and blood pressure did not have normal distribution, while others (gender, height, and BMI had normal distribution.

Baseline characteristics showed that most subjects were female (84.4%). Median age was 52 (40-60) years old. Other parameter anthropologic showed that more than half (53.1%) had normal weight, and mean BMI was 25.7 (17.3-34.2) kg/m^2. Almost one third (28.1%) of the subjects were hypertensive (table 1).

Table 1. Baseline characteristics

Variables	n=32	
	Mean±SD	Median (min-max)
Age (years)		52 (40 – 60)
Gender, n(%)		
Male	5 (15.6)	
Female	27 (84.4)	
Anthropometric parameters		
Height (cm)*	153.0±7.0	
Weight (kg)		59.5 (36.0 – 83.0)
BMI (kg/m^2)		25.7 (17.3 – 34.2)
BMI classification, n (%)		
Normoweight	17 (53.1)	
Overweight	12 (37.5)	
Obese	3 (9.4)	
Hypertension, n (%)	9 (28.1)	

n=number; %=percentage; SD=standard deviation; * mean±SD; BMI=body mass index;

Table 2. HbA1C level and CIMT

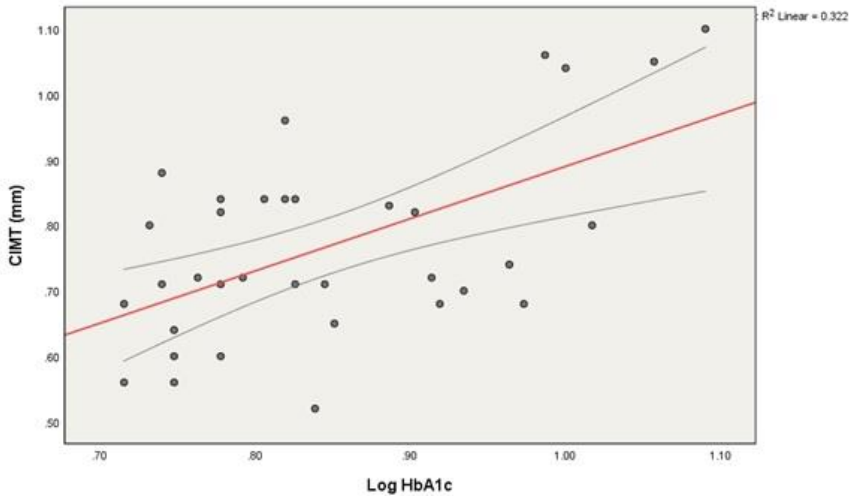
Variables	n=32	
	Mean±SD	Median (min-max)
HbA1c (%)		6.7(5.2–12.3)
CIMT (mm)	0.77±0.22	

SD=standard deviation; * mean±SD
HbA1C= Hemoglobin A1c; CIMT= Carotid intima-media thickness

Table 3.Correlation analysisHbA1c level withCIMT

	CIMT P Max (mm)			
	Correlation coefficient (r)	95% CI	p-value	Determinant Coefficient (R^2)
Log HbA1c	0.567	0.279 – 0.755	<0.001	0.322

r=0.567(0.4-0.599= moderate correlation); *p value <0.05 significant correlation; R^2=coefficient determination



Figures 1.Scatterplot showing correlation of HbA1C with CIMT

Saphiro-Wilk normality test showed anormally distributed CIMT values, while HbA1c had non-normal distribution. The mean CIMT was 0.77±0.22 mm, while the median HbA1c was 6.7 (5.2–12.3).

Pearson correlation analysis showed that there was a moderate positive correlation between HbA1c (log transformation) with CIMT (r=0.567, p<0.001) (table 2). The scatter plot illustrated a positive linear trend between HbA1c with CIMT (figure 1).

DISCUSSION

Baseline characteristics of the subjects showed a statistically significant gender difference (84.4% female vs. 15.6% male). An epidemiological study by Forouhi et al.described that gender had no significance in T2DM prevalence.[8] Both gender were found to have the same annual prevalence increment. The study result was similar to the data obtained by WHO regarding gender and T2DM prevalence.

Known risk factors for T2DM were genetics, ethnicity, history of gestational diabetes, old age, abnormal BMI, imbalance dietary pattern, and physical inactivity. Framingham study had previously shown a similar risk between male and female propensity toward cardiovascular event, whereas Riskesdas 2013 data stated that there were no statistically significant difference in T2DM

incidence based on gender (1.7% for female vs 1.4 for male).[9,10]

The baseline BMI in this study showed a median of 25.7 (17.3-34.2) kg/m^2. More than half (53.1%) had normal weight whereas 37.5% were overweight, and the other 9.4% were obese. This was opposed to WHO and IDF data, stating that the increase of prevalence of T2DM was in accord to the increase of abnormal BMI (obesity and overweight), and physical inactivity.[2,11] The increase in fat mass in abnormal BMI, either obesity or overweight state, was shown to impair insulin activity on glucose storage and uptake to cellular level, and was termed insulin resistance.[3,12] Study by Ernande et al., Zhang et al., Magdy et al,, and Leung et al. showed BMI abnormality with results of 29±5kg/m^2, 25,2±3.1kg/m^2, 29.13±3.14 kg/m^{2}34±8 kg/,respectively.[13-16]

The prevalence of hypertension in this study was found at 28.1%. This was similar to the finding by Ernade et al (38%), but far lower than those of Nakai (78%), Zhang (48%), and Leung (69%).[14.15,17-19]. The meta-analysis by Colosia et al. and Kabakov et al. showed the hypertension prevalence of over 50%.[20,21]

To our knowledge, there is currently no study investigating the correlation between CIMT and HbA1c in newly diagnosed T2DM patients. We found the HbA1c median of 6.7 (5.2–12.3)%, and CIMT of 0.77±0.22 mm. Multiple studies by Kawamori et al., Geroulakos et al., and Mohan et al. showed that mean CIMT in diabetic patients were higher than non-diabetic patients.[22-24] Other studies showed that mean CIMT in diabetic subjects was 0.82±0.22 mm and 0.95±0.31 mm whereas in non-diabetic subjects were 0.66±0.13 mm and 0.74±0.14 mm, respectively.[21,24] Other studies by McnNeely et al., Hung et al., and Venkataraman et al. investigated the association between HbA1c with CIMT in nondiabetic subjects of various ethnicity shown a consistent relation between the increase of CIMT and HbA1c in.[7,25,26]

Study by Lee et al. toward elderly population (mean age 71.8 years-old) in Korea found that mean HbA1c was 5.5% and mean CIMT was 0.9 mm, demonstrating that HbA1c was independently associated with increase in CIMT ((β=0,020, p=0,045).[7] Multiethnic (whites, Asia-America, Afro-American, and Hispanic) study by McNeely et al. showed that a higher HbA1c (6±0.3%) compared to lower HbA1c (5±0.2%) correlates with higher CIMT values (0.87 vs. 0.85 mm, p=0.003) respectively.[25] In T2DM patients, a cohort study by Yamasaki et al. in T2DM showed that at initial measurement, HbA1c was 8.66±0.1, with subsequent measurement after two-years follow-up was 8.15±0.08, revealed an increase in CIMT from initial measurement versus at two-years follow-up from 0.04±0.004 mm/years. The study concluded that mean HbA1c was an independent progressivity predictor of two-years CIMT increase (p<0.001).[28]

As previously stated, this study was the first to investigate the relationship HbA1c and CIMT in newly diagnosed T2DM, resulting in a moderate positive correlation (r=0.567; p<0.001). We infer that the higher HbA1c, the higher the CIMT will be. The unknown duration of DM prior to diagnosis was the main weakness in this study. Theoretically, insulin resistance and hyperglycemia may have manifested far before T2DM was diagnosed, thus resulting in disease progressivity. This, in part, supports the previous study results regarding CIMT and HbA1c in either diabetic or non-diabetic patients.[7,22-27].

The HbA1c as glycemic parameter indicates a chronic hyperglycemic state, and is utilized as primary complication predictor in diabetes based on study results and global diabetes guidelines. Hyperglycemia induces oxidative stress resulting in increased reactive oxygen species(ROS) formation and triggered cell injury mediated mainly through four molecular mechanisms.[29-31]

Hyperglycemia is also associated with the production of free fatty acids (FFA) and growth factors, leading to cellular metabolism abnormality. This will ultimately lead to endothelial and mitochondrial damage, producing ROS and disturbing genetic expression and nitric oxide production.[30] Aside from insult

by hyperglycemia, endothelial dysfunction may result from multiple factors such as cigarette smoke exposure and abnormal lipid level.[31]

These factors will increase endothelial ROS production that will interact with other intracellular molecular substances, and disrupting endothelial metabolic and synthetic function. Furthermore, endothelial dysfunction will trigger lipoprotein accumulation in intimal surface.

These LDS particle will aggregate on thickening intimal surface rich in proteoglycans, signifying first signs of atherosclerosis.[29-31] Multiple studies showed that glycemic parameters has positive correlation with oxidative stress. A high degree of DNA and oxidative stress were thought to occur in newly diagnosed T2DM patients as stated by the results of previous studies.[36-38] Other study showed a statistically significant correlation between DNA damage with hyperglycemia and insulin resistance.[3]

The HbA1c and CIMT as glycemic parameters in this study were found to have moderate positive correlation ($r=0.567$; $p<0.001$) with determinant coefficient (R^2) of 0.322. This means CIMT was affected by HbA1c to the extent of 32.2%, and the remaining was affected by other factors.

As stated in previous studies, CIMT is affected by various traditional risk factors namely, race, smoking, alcohol consumption, daily activity, dietary pattern, dyslipidemia, medications, hyperuricemia, and several novel risk factors such as inheritance, certain genotypes and anthropometric parameters, rheumatoid arthitis and other certain immunologic and inflammatory diseases, infection, vitamin D, matrix metalloproteinases, and many other under research factors.[39.]

We admit that the weakness of this study is inability to measure and put into considerations of other factors affecting CIMT in T2DM patiens.

CONCLUSION

There is a positive correlation between HbA1c level with CIMT in newly diagnosed T2DM patients.

DISCLOSURES AND ETHICS

No potential conflict of interest in this study.

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